REMARKS

The Abstract

The Abstract is identical to the Abstract submitted for parent application Serial No. 07/415,354 which application is incorporated by reference into the instant application. Because this Abstract was a part of the parent application it is urged that it presents no new matter.

The Drawings

The Applicant takes note of the fact that informal drawings have been filed. Formal drawings will be filed following receipt of a Notice of Allowability.

Amendments to the Specification

The amendments to the specification were to correct numerous obvious typographical or grammatical errors.

Rejections Under 35 U.S.C. § 103

In the most recent Office Action received for this application, the Office Action being that mailed 21 July 2000 for parent application 08/873,318, claims 49-62 (now claims 17-30) were rejected under 35 U.S.C. § 103 over Essex et al. in view of Tungkanak et al. and Vander-Mallie.

The claims require the selection of a prototypic set wherein the prototypic set are antibodies which bind to an aetiological agent of interest. The Office Action mailed 15 March 1999, in responding to the statements set forth in the Preliminary Amendment filed 28 December 1998, states that the prior art teaches separating antibodies into groups. Such groups are not the same as required by claim 49. Claim 49 requires that the prototypic set consist of antibodies which bind to an etiological agent, these having been selected from all antibodies being present (e.g., selecting from a serum sample only those antibodies which bind to the etiological agent). The Essex patent does not disclose such a step. In Example 1, parts A-C, the patent teaches simply making an extract of cells infected with HTLV in order to have an extract which contains an etiological agent (in particular, glycoproteins of 61,000-68,000 Daltons). Part D of Example 1 is the same as Parts A-C except that the glycoprotein is deglycosylated to form a protein of molecular weight 45,000-52,000

Daltons. In part E of Example 1, antibodies present in a variety of serum samples are bound to beads. Some of the serum samples are from persons infected by HTLV and therefore contain antibodies to the 61,000-68,000 Dalton glycoprotein or 45,000-52,000 Dalton protein of HTLV. These sera from HTLV infected persons also contain antibodies to many antigens other than the stated glycoprotein or its deglycosylated form. Other serum samples are from uninfected persons and do not contain antibodies to the HTLV glycoprotein or its deglycosylated form, but they do contain antibodies to other antigens. In step E, following the binding of antibodies to beads, the cell extracts of parts A-D are mixed with the beads. Those beads which have bound serum samples containing antibodies to HTLV bind the antigens (i.e., the 61,000-68,000 Dalton glycoprotein or the 45,000-52,000 Dalton protein) in the cells extracts. Those beads which bound serum samples from uninfected persons do not have the necessary antibodies and therefore do not bind the HTLV antigens (specifically they do not bind the 61,000-68,000 Dalton glycoprotein or 45,000-52,000 Dalton protein). Step E continues by washing away unbound material then eluting the antigens which did bind to the beads. The bound antigens are then analyzed in part F of Example 1. This is the only Example in the whole patent disclosure of Essex. Nowhere was there a selection of antibodies. Instead, the only step concerning antibodies was Step E and there all of the antibodies from sera were bound to beads. Thus all antibodies were used without a selection step. This means antibodies were present which did not bind to the HTLV antigens. The claims as they presently stand require that a selection step occurs to select only those antibodies which bind to the desired antigen (etiological agent). Consequently, the Essex disclosure lacks a teaching of a step required by the claims of the instant invention.

The Office Action also states that Vander-Mallie teaches separation of antibodies into different groups, that reference teaching that "antibodies produced in response to immunization can be utilized as serum, ascites fluid, an immunoglobulin (Ig) fraction, and IgG fraction, or as affinity-purified monospecific material". Again, these groups are different from the prototypic group of antibodies prepared by the method of claim 49.

The selection step is not merely a step in the claims but is really the concept of the invention. Rather than making anti-antibodies to all antibodies present, one is first selecting those antibodies which bind to the antigen of interest and then making anti-antibodies only to those. This results in

production of desired anti-antibodies rather than a complex mixture of anti-antibodies most of which may not be desired because these undesired anti-antibodies were produced against antibodies not of interest. Since one consequently produces a much purer product containing those anti-antibodies of interest, this product is much more likely to be active for the desired purpose, e.g, for use as a vaccine.

It is urged that the above arguments show that the cited prior art does not teach all the steps of the claims as they presently stand. Furthermore, the steps of the claims which do distinguish the claims from the prior art are critical to the invention. The cited prior art does not teach the type of prototypic set required by the claims and does not suggest making such a prototypic set or suggest any reasons for making such a prototypic set. The groups of antibodies taught by the prior art are very different from the prototypic set of antibodies taught by the disclosure and required by the claims of the instant application.

In view of the amendments to the specification and the claims and in view of the above remarks, it is urged that the claims satisfy the provisions of the patent statutes and are patentable over the prior art. Reconsideration of this application and early notice of allowance are requested. The Examiner is invited to telephone the undersigned to expedite allowance of this application.

Respectfully submitted,

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Amended Page 3, Paragraph on Lines 14-24: Version with markings to show changes made

Each antibody comprises a glycoprotein molecule. The portion of an antibody molecule embodying the characteristic of shape or molecular topography, or code sequence which enables it to bind and so for example neutralise the antigenic determinant or epitope of an antigen is known as a "paratope". The paratope is conceptually a molecular region of a shape [complimentary] complementary to the epitope or to a part of the epitope of the antigen and is thought to reside in the so called hypervariable region of the antibody glycoprotein molecule.

Amended Page 6, Paragraph on Lines 10-12: Version with markings to show changes made

According to one aspect [of] the present invention consists of a method of treating an animal comprising the steps of:

Amended Page 7, Paragraph on Lines 10-13: Version with markings to show changes made

According to a second aspect the present invention consists [in] of a method of manufacture of an anti-paratopic antibody efficacious against mammalian infections comprising the steps of:

Amended Page 8, Paragraph on Lines 23-26: Version with markings to show changes made

The antibodies, or paratypic paratope bearing segments of them, are utilized as [a] an immunogen in a mouse host to produce mouse antibodies having anti-paratope characteristics.

Amended Page 9, Paragraph on Lines 20-21: Version with markings to show changes made

Figure 5 (II) [illustrated] illustrates a general procedure for the purification of HIV antigen specific human antibodies.

Amended Page 9, Paragraph on Lines 25-27: Version with markings to show changes made

Figure [6 (a)] 6a illustrates purification of human IgG prior to delineation into HIV/HIV antigen specific antibodies.

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Figure [6 (b)] 6b illustrates purification of human IgA prior to delineation into HIV/HIV antigen specific antibodies.

Amended Page 10, Paragraph on Lines 4-6: Version with markings to show changes made

Figure [6 (c)] 6c illustrates purification of human IgM prior to delineation into HIV/HIV antigen specific antigens.

Amended Page 10, Paragraph Beginning on Line 27, through Page 11, Line 22: Version with markings to show changes made

Secondly, the present invention has as its basic premise the observation that epitope presentation within a particular species is unique to that species. The prior art technology looks to immuno-dominant epitopes common to all species and aims to produce mirror images to them. Epitopes selected in the prior art technology are identified using empirical approaches and numerous [algorithums] algorithms have been used to predict antigenic sequences. In the present invention, antigenic sequences necessary to produce neutralizing epitopes are believed to be both linear and assembled. Antigen presentation is a multifactorial operation involving several host immune components. Hence, the basic premise of the present invention is that epitope mapping algorithms while applicable do not identify all epitopes of immunological significance. It is in this area which the present invention is focused. The host immune system has a role in the amplification and display of the total [repertorie] repertory of epitopes of the invading immunogen. The present invention capitalises on this factor whilst prior art technologies have tended to approach the problem from a more conventional anti-idiotypic approach.

Amended Page 12, Paragraph Beginning on Line 8, through Page 13, Line 4: Version with markings to show changes made

Finally, both the present invention and anti-idiotypic technology use hybridoma technology, protein chemistry and immunology. When testing the putative vaccine, however, anti-idiotype vaccines have to be tested for [complimentary] complementarity and efficacy in several animal

species e.g. rabbits, sheep, baboons or chimpanzees etc. This is necessary to compensate for the interspecies approach used to generate and test the vaccine candidate. This is a relatively long and time consuming step. The vaccine candidate produced in the present invention, however, has to be tested primarily for [complementary] complementarity within the species to be immunized. It is designed to be primarily an intra-species approach. Accordingly, from a small pool of infected individuals either immune to a particular infectious agent or carrying neutralizing antibodies to it and using standard techniques (or minor technological variants) to produce anti-paratopic antibodies, it is possible using the present invention to generate specific vaccines against said infectious agent. These vaccines can then be used to treat a small number of infected individuals or to immunize an entire population of individuals prone to infection by said infectious agent.

Amended Page 13, Paragraph on Lines 5-21: Version with markings to show changes made

The particular advantage of the present invention is that in the case of some viruses, for example AIDS, there are so many epitopes some of which are protective, some of which are suppressive, some of which are dominant and some which have no [affect] effect on the immune system. In the present invention, selection of the antibody is not dependent on the epitope. Instead, selection is based on whether the antibody produced is neutralizing or not. In contrast, in prior art approaches, antibody selection depends on an epitope being common to a variety of different species. For example, if an antibody works in rabbits but not in guinea pigs, it is discarded. The result being to reject it but in doing so, the very epitopes which could protect human populations may be lost. This is overcome by the present invention because reliance is not placed on epitope recognition between species.

Amended Page 14, Paragraph on Lines 13-20: Version with markings to show changes made

In the example under consideration the first stage is to select from the pool of human antibodies a prototypic set, in this case a set of immunoglobulins which effectively bind the aetiologic agent for Acquired Immune [Deffiency] Deficiency Syndrome (AIDS). The generally accepted aetiological agent for AIDS is currently known as Human Immunodeficiency Virus hereinafter referred to as HIV.

Amended Page 15, Paragraph on Lines 3-4: Version with markings to show changes made

If desired the retained immunoglobulin members so selected may be purified [an] and used directly in step (3).

Amended Page 17, Paragraph on Lines 9-13: Version with markings to show changes made

The human IgG/A/M is drawn from three main groups affected by AIDS viral infection, viz

- male homosexuals
- bisexual/female/heterosexual AIDS carriers
- [haemophilics] hemophiliacs

Amended Page 18, Paragraph on Lines 10-21: Version with markings to show changes made

Alternatively, the Ig sub-classes may be screened to select antigen specific antibodies for use as the immunogen. In this case, the Ig sub-classes are next screened for effectiveness against HIV antigen to select the most effective sub-classes in binding the antigen. More preferably, the antigen is first divided into sub-classes known as p18, p24, gp41, p55, gp120 and gp160. These antigen sub-classes differ from each other in molecular structure and can be separated by SDS-polyacrylamide gel [electrophoresus] electrophoresis. Each Ig sub-class is then screened against each antigen sub-class to select the most effective Ig's.

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Table 2

HTLV III - HUMAN SERUM [1g] Ig PARATOPE GRID

Amended Page 20, Paragraph Beginning on Line 25, through Page 21, Line 6: Version with markings to show changes made

Human antibodies are excellent immunogens when injected into mice. The antigenic sites on the human antibody molecules are spread right across the length of the molecule from the NH_2 [terminii] terminus-ie the Fab end to the carboxylic acid terminus -ie the Fc end. The Fab NH_2 end carries the paratope. Other antigenic components of the Fab are present for structural or "carrier"

purposes. For the purposes of the vaccine the Fc exclusively exhibits "carrier" as opposed to paratope antigens.

Amended Page 21, Paragraph Beginning on Line 7, through Page 22, Line 6: Version with markings to show changes made

Immunization studies have demonstrated that not all the antigenic sites on the intact human immunoglobulin molecule are of equal value in that a greater proportion of induced antibodies tend to be directed against the Fc region. This [phenomena] phenomenon is described as antigenic competition or more accurately as intramolecular antigenic competition. When developing an anti-paratopic antibody, however, the part of the molecule of most interest is the Fab area that is to say the paratope bearing region. A simple way to overcome the problem of Fc dominance is to enzymatically cleave the immunoglobulin molecule and isolate the Fab fragment. When used to immunize a mouse this will cause all the induced immunoglobulins to be directed against the Fab fragment. A subset of the anti-Fab antibodies generated by the mouse, irrespective of whether an intact immunoglobulin molecule or a Fab/F(ab)'2 fragment has been used, will be directed against the internal idiotope i.e. paratopic image of the human immunogen. Thus, the member of the anti-HIV prototypic set used as an immunogen in the mouse may be either (a) the mixed intact human immunoglobulin specific for the AIDS virus, (b) selected classes or sub-classes of the intact immunoglobulin, (c) a Fab/F(ab)'2 fragment of one or a combination of the AIDS specific immunoglobulins or (d) a Fab/F(ab)'2 fragment of one or a combination of the AIDS specific immunoglobulins complexed to [carries] carriers eg. Keyhole Limpet Haemocyanin or human albumin.

Amended Page 33, Paragraph on Lines 24-27: Version with markings to show changes made

(ii) given the diversity of the immunoglobulin response the antibody range may not be restricted and a more general immunization routine adopted. In the latter case[.]

Amended Page 24, Paragraph on Lines 7-9: Version with markings to show changes made

While stating a preference for (i) an outline of the various alternative pathways for the purification and preparation of the immunogen is shown [if] in Figs. 5 and [6] 6A-C.

Amended Page 30, Paragraph on Lines 9-12: Version with markings to show changes made

Sub genomic clones of HIV cDNA encoding gp120, gp41, p24 and p18 were cloned and amplified in [E. coli] *E. coli* using λ gt11. The [E. Coli] *E. coli* lysates were screened with in-house and by commercial HIV antigen ELISA's.

Amended Page 30, Paragraph on Lines 17-26: Version with markings to show changes made

Following precipitation of [E. Coli] *E. coli* antigens with $(NH_4)_2SO_4$ the supernate was concentrated (Amicon) dialysed against distilled water and then against 0.05M Phosphate buffer pH7.2 (16hrs, 4°C). 40 mls of the dialysed concentrate was combined with approximately 2 ml of the IgG-Sepharose and the mixture incubated end-over-end for 2 hrs (RT). The matrix was exhaustively washed and the recombinant protein eluted using 4M $MgCl_2$, pH 8.3. The presence of recombinant antigen was confirmed as outlined above.

Amended Page 32, Paragraph on Lines 14-25: Version with markings to show changes made

Mouse Ab2 antibodies were induced in the following way. 1.3 x 10^8 mouse spleen cells were recovered and washed in the incubation medium (Iscoves DMEM medium containing 20% foetal calf serum (FCS), 40% thymus conditioned medium (TCM), 5 x 10^{-4} M 2-mercaptoethanol, [4mML-glutamine] 4 mM L-glutamine 50 IU Penicillin and 50 IU streptomycin). HIV specific human immunoglobulins at a concentration of 10 micrograms/ml incubation medium was added to the mouse spleen cells. The total volume used in the incubation of the spleen cells with human antibody varied between 10 and 15 mls. In this example, the incubation was allowed to proceed for 7 days in a heated (37°C) CO_2 incubator.

Amended Page 32, Paragraph Beginning on Line 27, through Page 33, Line 10: Version with markings to show changes made

Following incubation the cells were recovered for fusion to [ether] either SP2, NS1 or X63-Ag*.653 mouse myeloma cells. The viability of the spleen cells was found to vary between 70 and 99% and the viability of the myeloma was generally 99%. For the sake of illustration SP 2 mouse spleen cells were used though other cells such as rat or human myeloma cells could be used in this procedure. Spleen cells were fused to the myeloma cells using polyethylene glycol 1500/4000 (Boehringer/Mannheim) using standard procedures and following 24 hrs incubation in a CO_2 incubator at 37°C the hybrids were plated out in the incubation medium now containing HAT.

Amended Page 34, Paragraph on Lines 11-14: Version with markings to show changes made

Human peripheral blood lymphocytes (PBL's) were diluted 1:1 in phosphate buffered saline and the red cells removed by centrifugation through a Ficoll-hypaque cushion ([pharmacia] Pharmacia).

Amended Page 34, Paragraph Beginning on Line 15, through Page 35, Line 2: Version with markings to show changes made

The PBL's either depleted or not depleted of monocytes and lymphocytes using methods familiar to those skilled in the art, were then transformed using for example the EBV isolate B95-8 in sterile tissue culture media (RPMI-1640[]] + 5% FCS). In a simple example the B95-8 isolate is made available as a supernate which is mixed with the monocyte/T cell depleted fraction enriched for the B lymphocytes. The cells are grown in this mixture, fed as required, and expanded in 96-well flat bottomed plates prior to fusion with the mouse myeloma cell line such as X63-Ag*.653. Screening is by a commercially available HIV antibody ELISA. Cloning and feeding (Medium containing HAT/HT) is by the usual method except that non transformed will be selected out by feeding with 1 micromolar Oubain.